

# Monitoring of Urinary Calcium and Phosphorus Excretion in Preterm Infants: Comparison of 2 Methods

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## ABSTRACT

**Objectives:** Premature babies require supplementation with calcium (Ca) and phosphorus (P) to prevent metabolic bone disease of prematurity. To guide mineral supplementation, 2 methods of monitoring urinary excretion of Ca and P are used: urinary Ca or P concentration and Ca/creatinine (Crea) or P/Crea ratios. We compare these 2 methods in regards to their agreement on the need for mineral supplementation.

**Methods:** Retrospective chart review of 230 premature babies with birth weight <1500 g, undergoing screening of urinary spot samples from day 21 of life and fortnightly thereafter. Hypothetical cutoff values for urine Ca or P concentration (1 mmol/L) and urine Ca/Crea ratio (0.5 mol/mol) or P/Crea ratio (4 mol/mol) were applied to the sample results. The agreement on whether to supplement the respective minerals based on the results with the 2 methods was compared. Multivariate general linear models sought to identify patient characteristics to predict discordant results.

**Results:** A total of 24.8% of cases did not agree on the indication for Ca supplementation, and 8.8% for P. Total daily Ca intake was the only patient characteristic associated with discordant results.

**Conclusions:** With the intention to supplement the respective mineral, comparison of urinary mineral concentration with mineral/Crea ratio is moderate for Ca and good for P. The results do not allow identifying superiority of either method on the decision as to which babies require Ca and/or P supplements.

**Key Words:** calcium, dietary supplement, metabolic bone disease, phosphorus, preterm infant

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Premature babies miss the period of greatest mineral accretion during the last trimester of pregnancy, when 60% and 80% of whole-body calcium (Ca) and phosphorus (P) are transferred actively from mother to fetus. This parallels an exponential increase in bone formation between 24 weeks' gestation and term (1). After premature birth, deficiency of Ca and P caused by insufficient nutritional supply and relative immobilization presents unfavorable circumstances for the growth and mineralization of bone. Aggravated by severe illness and medication, metabolic bone disease of prematurity (MBDP) can develop.

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Treatment of Ca and P deficiencies and preventive measures of MBDP result in the improvement of growth and bone mineral content until 1 year of age (2,3), albeit not into adolescence or early adulthood (4). To achieve a bone mineral accretion rate similar to intrauterine level, individual requirements may not be met by standardized fortified breast milk (5). Thus, the concept of monitoring and individual supplementation of Ca and P arose in the early 1990s (2). Indiscriminate supplementation does not account for variable intestinal absorption (6) and may pose risks, for example, development of nephrocalcinosis, possibly accentuated by medications such as furosemide or steroids (7). Varying monitoring tools are used across the different neonatal units, leading to inconsistent practices (8).

Urinary mineral excretion in spot urine samples has been shown to be a valuable and easy means for adjusting supplementary intake of minerals (2,9). Two methods of measuring urinary excretion are used: pure urinary Ca and P concentrations (millimoles per liter or milligrams per deciliter) or urinary calcium/creatinine (Ca/Crea) and phosphorus/creatinine (P/Crea) ratios (mole per mole or gram per gram). Despite the debate on the preferred method of monitoring (10), no direct comparison of these 2 concepts has been made with regard to determining Ca and P supplementation. This retrospective study investigates whether the intention to supplement minerals is affected by the method of measurement of urinary Ca and P excretion (pure Ca and P concentration vs Ca/Crea and P/Crea ratio).

## METHODS

This study was performed in the neonatology unit of the Children's University Hospital, Bern, Switzerland, the regional tertiary neonatal referral center. The local institutional review board approved the collection of the retrospective data.

Starting on day 21, urine samples are obtained from babies with birth weight <1500 g as part of the routine metabolic screening. This is repeated every second week thereafter, until reaching a body weight of 2500 g or discharge (whichever occurs first). To keep the screening process noninvasive and in view of the scarce evidence for the usefulness in detecting the need for mineral supplementation (9,11), the local protocol does not routinely request serum parameters for bone health (ie, serum Ca, P, alkaline phosphatase, vitamin D) to be analyzed alongside the urinary measurements. In this retrospective chart review, data for all babies qualifying for screening between January 2003 and September 2006 were analyzed. Exclusion criteria were the use of diuretics at the time of sample collection as a factor influencing calciuria (12,13), and incomplete datasets. Even though methylxanthines (caffeine and theophylline) also influence calciuria, indirect evidence suggests that their calciuric effect is weaker than that of diuretics (14); hence, patients receiving methylxanthines at the time of spot urine sampling were included in the study. At the start of screening, all included children were fed enterally (either fortified breast milk [FM85, Nestlé, Vevey, Switzerland] or preterm formula

[Beba Alprem 16% or 17%, Nestlé] and received 400 IU of vitamin D (Cholecalciferol, Oleovit, Fresenius Kabi, Graz, Austria) as well as 225 IU (for weight <1500 g) or 500 IU (for weight >1500 g) of ergocalciferol through a multivitamin preparation (Oranol, Bayer, Zurich, Switzerland) orally.

Urine samples were analyzed in an automated modular analyzer (MODULAR Cobas P800, Roche/Hitachi Diagnostics, Mannheim, Germany) at the central pathology service of our university hospital. The following methods were used for analysis (with respective coefficient of variation [CV]): colorimetric assay with *o*-cresolphthalein complexon for urinary Ca (CV 0.8%), ultraviolet test on ammonium phosphomolybdate complex for urinary P (CV 0.7%), enzymatic method based on conversion of Crea by creatininase, creatinase, and sarcosine oxidase for urinary Crea (0.8%).

We applied hypothetical cutoff values to the results of urine samples to determine the need for Ca and P supplementation. We chose 1 mmol/L as the lower cutoff for both urinary Ca and P concentration because this value is suggested in the only study that used bone mineral content as an endpoint (2,10). We did not find reference values for Ca/Crea or P/Crea for preterm babies in the literature relating to bone mineral content (or other endpoints). Only 1 study describes the trends of urinary mineral/Crea ratios in P-supplemented preterm infants (15). In the absence of endpoint-tested reference values, the 10th percentile from the percentile curves of the aforementioned study were extrapolated for Ca/Crea and P/Crea and used as lower cutoff values: Ca/Crea 0.5 mol/mol and P/Crea 4 mol/mol. The authors rated the value for Ca/Crea in keeping with values reported in other studies (9,16–18), although none of these studies have been set up to search reference values, but merely report values found in cohorts of similar age to our study population. For P/Crea, no references for preterm infants could be found in either original articles or textbooks, because percent of tubular reabsorption is ordinarily used to assess renal excretion of P (19). Therefore, the authors agreed upon the above value.

We produced log-log scatterplots and added lines representing the cutoff values to visualize the agreement of the 2 methods regarding indication for mineral supplementation. Numerically, the agreement was expressed as Cohen  $\kappa$ . We built multivariate general linear models to identify patient characteristics that predict discordant results. The candidate predictors in the model included Ca intake, P intake (to account for type of feeding), total daily fluid intake, total daily protein intake, gestational age at birth, post-menstrual age at the time of measurement, birth weight, weight at time of measurement, number of days of ventilation, number of days of noninvasive ventilation (continuous positive airway

pressure), days of supplemental oxygen, days of parenteral nutrition (PEN) (the latter 4 parameters representing surrogate markers for the degree of illness of the baby), and treatment with caffeine at the time of urine sampling. To account for correlated data arising from repeated measurements within patients, we fitted generalized estimation equation models for the binary data using the logit link function. Statistical analyses were performed using the software package SAS 9.2 (SAS Institute Inc, Cary, NC).

## RESULTS

### Patient Characteristics

A total of 230 preterm babies (52% girls) were included in the study. Median gestational age at birth was 29 weeks + 1 day (range 23 + 6 to 36 + 4) with median birth weight of 1133 g (range 420–1530). Details of the medical treatment received during the stay in the neonatal intensive care unit are summarized in Table 1. Generally, the patients required invasive ventilation for a short period and reached full feeds after a similar time range (implied by number of days on PEN). The babies included in the study underwent a median of 2 (range 1–10) urinary screenings.

### Calcium

Median urinary Ca concentration was 1.2 mmol/L (range 0.05–10.2) and median Ca/Crea ratio was 1.4 mol/mol (range 0.05–9.8). Of a total of 593 urine samples, Ca supplementation would have been indicated in 237 (40.0%) based on the measurement of urinary Ca alone. A total of 91 samples (15.5%) would have qualified for additional Ca supplementation using the Ca/Crea ratio. Figure 1 shows that disagreement between the 2 methods was found in 146 (24.8%) of all samples when urinary Ca concentrations, but not Ca/Crea, were below the cutoff values; however, there was no case that qualified for supplementation through a Ca/Crea ratio of <0.5 mol/mol wherein the urinary Ca concentration was above the cutoff of 1 mmol/L at the same time. The agreement between the 2 methods was poor ( $\kappa = 0.43$ , 95% confidence interval 0.36–0.49). Median urinary Ca in the discordant range (upper left quadrant in Fig. 1) was higher (0.68 mmol/L, range 0.23–0.99) compared with the median urinary Ca in the lower left quadrant, where methods agreed (0.28 mmol/L, range 0.05–0.93).

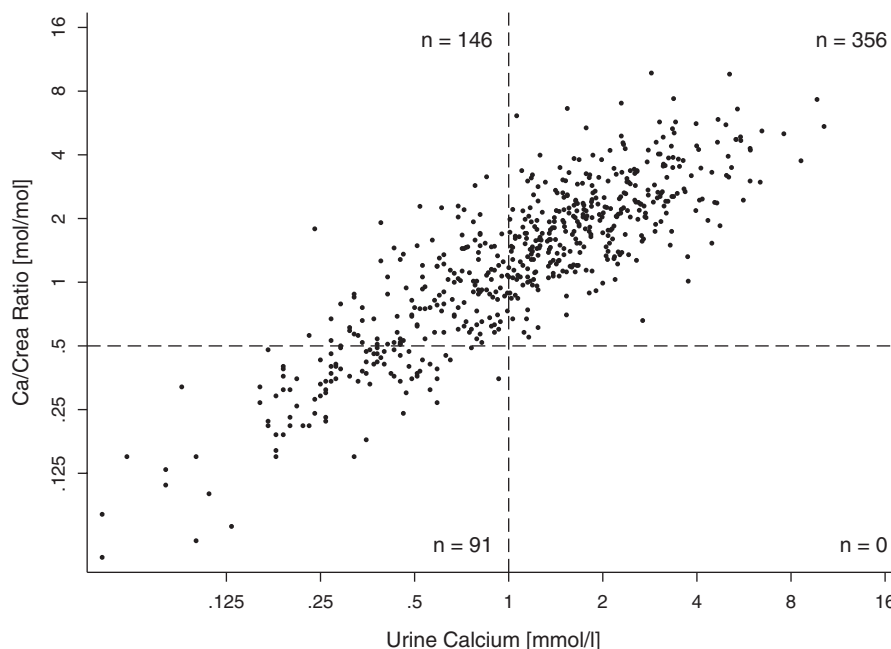
In the multivariate analysis, only Ca intake was a statistically significant predictor of discordant results between the 2 methods. This means that a high Ca intake was associated more often with a urinary Ca concentration below the cutoff of <1 mmol/L as well as

TABLE 1. Patient characteristics and medical treatment for 230 study subjects by gestational age

	<28 wk, n = 67 (29%)	28–32 wk, n = 132 (57%)	>32 wk, n = 31 (14%)	Total, n = 230
SGA n (% of group)	11 (17)	34 (26)	26 (84)	71 (31)
Ventilation n (% of group)	55 (82)	84 (64)	14 (45)	153 (67)
Median days (range)	2 (1–54)	1 (1–26)	1 (1–5)	1 (1–54)
CPAP n (% of group)	65 (97)	124 (94)	16 (52)	205 (53)
Median days (range)	35 (2–86)	7.5 (1–47)	2.5 (1–9)	12 (1–86)
Oxygen n (% of group)	66 (99)	124 (94)	21 (68)	211 (92)
Median days (range)	48.5 (1–137)	10 (1–141)	1 (1–8)	18 (1–141)
PEN n (% of group)	57 (85)	120 (91)	27 (87)	204 (89)
Median days (range)	11 (5–49)	9 (3–47)	8 (3–42)	9 (3–49)
Caffeine* n (% of group)	59 (88)	64 (48)	0 (0)	123 (53)

CPAP = continuous positive airway pressure; PEN = parenteral nutrition; SGA = small-for-gestational age (birth weight <10th percentile).

\* Treatment at any time.



**FIGURE 1.** Log-log scatterplots of urinary calcium (Ca) concentration (mmol/L) versus urinary Ca/creatinine (Crea) ratio (mol/mol). Dashed lines indicate cutoff values for supplementation: 1 mmol/L for urinary Ca concentration, 0.5 mol/mol for urinary Ca/Crea ratio.

a Ca/Crea above the respective cutoff of 0.5 mol/mol ( $P=0.045$ ). All other characteristics in the model did not predict disagreement.

## Phosphorus

Median urinary P concentration was 8.35 mmol/L (range 0.5–65.5). Median P/Crea ratio was 9.9 mmol/mmol (range 0.19–41.1). P supplementation would have been indicated in 53 of 593 urine samples (8.8%) based on urinary P concentration, and in 105 (17.7%) based on P/Crea ratio. In 52 samples (8.8%), the 2 methods disagreed and suggested supplementation as per P/Crea cutoff, but not as per urinary P concentration (Fig. 2). No sample was below the cutoff for urinary P concentration and at the same time above cutoff for P/Crea. Cohen  $\kappa$  of 0.63 (95% confidence interval 0.54–0.72) indicates good agreement between the 2 methods. As opposed to the results for Ca, none of the patients' characteristics in the multivariate analysis predicted whether the results of the 2 tests would disagree.

In our study population, urinary Crea concentration, urinary Ca and P concentration, and Ca/Crea and P/Crea ratios were not age dependent (either for gestational or chronological age) (Spearman correlation coefficient  $r < 0.16$ ).

## DISCUSSION

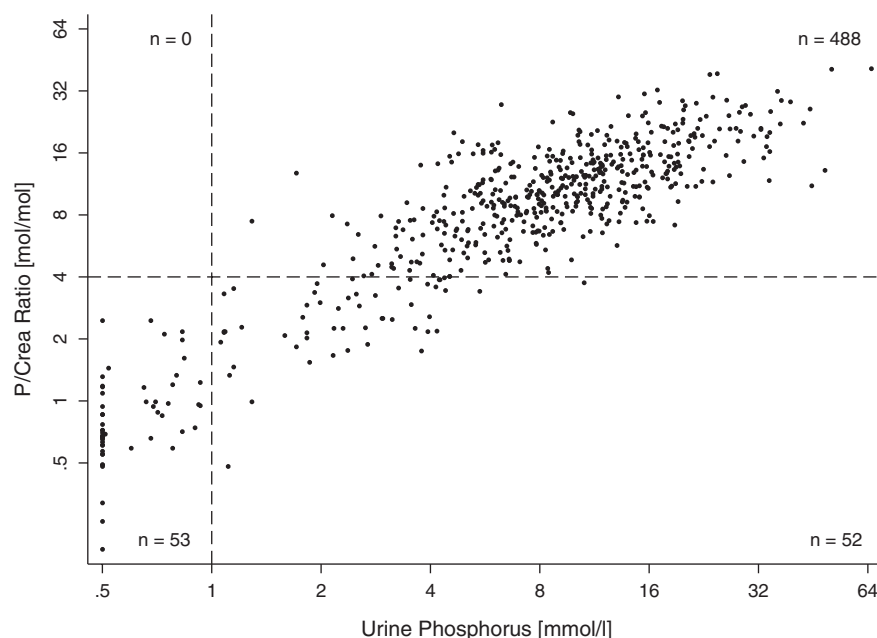
To prevent MBDP, premature babies may need supplementation of Ca and P in addition to fortified breast milk or specialized preterm formula. In this study, we compared the intention to supplement enteral Ca and P intake based on the 2 different measurement methods of mineral excretion in urine: pure urinary Ca and P concentration versus urinary Ca/Crea and P/Crea ratios. The 2 methods only moderately agreed for Ca, but more substantially agreed for P. In general, the characteristics of patients such as weight and age (at birth or time of measurements) and surrogate markers for their degree of morbidity (duration of ventilation, continuous positive airway pressure, supplemental oxygen, PEN)

did not show an association with the extent of concordance. The only exception was total Ca intake, which was higher in patients requiring additional Ca supplements according to the urinary Ca concentration, but not the Ca/Crea ratio.

The measurement of pure Ca and P urine concentration is based on the concept of slight surplus supply. According to this concept, a slight surplus of serum Ca and P allow for slight urinary excretion of Ca and P, proving indirectly sufficient serum levels, independent of age and weight of patient (2). Previously, supplementation adapted according to this concept suggested improved bone mineralization in premature infants by densitometry, although not in a prospective randomized design (2).

In contrast to the slight surplus supply, mineral/Crea ratios are used on the basis that Crea and mineral concentrations are inversely proportional to urine volume; hence, mineral/Crea ratio corrects for volume-induced changes in concentration. Aladangady et al (15) aimed to establish reference ranges for Ca/Crea and P/Crea ratios in a population of premature babies already supplemented with P. These values are the only longitudinal description of urinary mineral/Crea ratios during the neonatal period, but they have not been studied against bone mineral content as a primary endpoint.

Theoretically, mineral/Crea ratios should be superior to pure urinary mineral concentration because in children and adults, Ca/Crea and P/Crea are valid predictors of 24-hour Ca and P excretion (20,21); however, the usefulness of correction for volume-induced changes in premature infants has been contested (10). Because most stable preterm infants receive a constant daily fluid intake through feeding at regular intervals, no circadian variation in urinary concentrations of minerals is to be expected (22). Boehm et al showed that mineral/Crea ratios correlate poorly with the daily amount of excretion (23). Additionally, Rassin et al demonstrated an effect of dietary protein quantity and quality on Crea concentration in the urine of premature infants, whereas volume of daily fluid intake did not have any influence (24). These data suggest that the urinary Crea excretion is influenced by a



**FIGURE 2.** Log-log scatterplots of urinary phosphorus (P) concentration (mmol/L) versus urinary P/creatinine (Crea) ratio (mol/mol). Dashed lines indicate cutoff values for supplementation: 1 mmol/L for urinary P concentration, 4 mol/mol for urinary P/Crea ratio.

variety of factors. Therefore, caution should be exercised when using it in context with the excretion of other metabolites in premature babies.

In our study, increased total daily Ca intake was associated with a higher likelihood of requiring Ca supplementation through measurements of urinary Ca excretion, but not as per the Ca/Crea ratio. Indeed, median urinary Ca in the upper left quadrant of Figure 1 (where results disagree) is higher than in the lower left quadrant (where results agree), raising the numerator and thereby the total of the Ca/Crea ratio. Hence, although still requiring supplementation with a Ca concentration <1 mmol/L, the higher urinary Ca concentration increases the ratio sufficiently to place it above the cutoff for Ca/Crea and therefore not warrant supplementation according to this method. On the contrary, a clinical scenario in which increased Ca intake leads to decreased urinary Crea excretion (to decrease the ratio through a smaller denominator) is biologically implausible, especially because parameters described in other studies as influencing urinary Crea excretion such as weight, postmenstrual (25) and postnatal age (26), protein quantity, and type of nutrition (24) did not differ between the groups in our study.

Because no previous study has investigated the present comparison of Ca and P excretion, the question remains whether urinary Crea and thus mineral/Crea ratio adds additional information. Advocates for the slight surplus supply concept claim that the exact daily amount of mineral excretion is not as important as the concentration in spot urine samples, indicating sufficient supply to allow excretion in urine (10). Although attempts have been made to establish reference ranges for mineral/Crea ratios in premature infants (15), urine Crea and consequently the ratios are likely to be influenced by multiple factors (23,24).

The question of validity of either of the 2 screening methods is unlikely to be answered by the existing literature because there is no criterion standard against which the 2 methods of urine screening could be verified. No previous study has determined cutoff values for mineral supplementation or correlated either of the 2 urine screening methods with the presence or absence of MBDP in a

prospective design. In the absence of an accepted criterion standard, a meaningful accuracy study to report test sensitivity and specificity was not possible in our study. For the same reason, it would not have been reasonable to shift the cutoff values of the screening methods to optimize their agreement. Such a receiver operating characteristic analysis would require 1 of the 2 methods to be uplifted to the criterion standard, which is not appropriate. Therefore, we had to rely on previous studies reporting values of urinary mineral excretion in similar cohorts, which were designed to establish reference values or to correlate the values with bone mineral content or other meaningful endpoints.

The lack of an accepted criterion standard for the evaluated tests is an important limitation of our study. Future research needs to consider an alternative to the classical diagnostic accuracy paradigm. Clinical test validation, which measures associations between test results and relevant clinical outcomes, could be an answer to this difficult test evaluation situation (27). In the case of MBDP, quantitative ultrasound (tibial speed of sound) (28) or dual energy x-ray absorptiometry scans (29) have been used to diagnose and follow-up bone (de)mineralization in premature infants. By demonstrating an association between the results of either of the 2 methods of urinary screening and the endpoints in prospective studies, cutoff values for urinary mineral excretion could be established and mineral supplementation adjusted accordingly.

Our analysis did not show any relation of Ca or P excretion by either method with gestational or postnatal age. These results contrast the findings of Aladangady et al (15) of an inverse relation between Ca/Crea ratio and postnatal age (but not gestational age). The consistent weight-based P supplementation of the infants in Aladangady and colleagues' study population may have led to a concomitantly increased uptake of serum Ca into bone, paralleling a decreasing Ca excretion with age. Therefore, the correlation could reflect postnatal treatment rather than gestational maturity and render a comparison with our study population unfeasible. Other seemingly controversial results of studies examining associations between gestational or postnatal age and different measures of renal mineral excretion (26,30) emphasize the dependence of correlations

on local practices in terms of nutrition and mineral supplementation.

In conclusion, we report comparisons of urinary mineral excretion with mineral/Crea ratios with regard to Ca and P supplementation with moderate and good agreement, respectively. The present study does not allow identification of superiority of either method in recognizing premature babies requiring mineral supplements. Further research should concentrate on prospective studies to prove 1 of the 2 methods as a feasible monitoring tool, using total bone mineral content as an endpoint.

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